

IN THE SPECIFICATION

Please amend the specification as follows.

Please replace the Abstract with the Substitute Abstract submitted herewith.

Please replace the paragraph beginning at page 4, line 27 to page 5, line 2, with the following rewritten paragraph:

--Figure 2. To design the 1<sup>st</sup>—3<sup>rd</sup> generation glycopeptides they were illustrated as amphipathic  $\alpha$ -helical wheels (2 and 9 are shown). The hydrophilic residues are shown in red and the hydrophobic residues in blue. The message segment YtGF is not shown as part of the helix. The expected membrane position is shown as a line gray line.

Figure 3. Glycopeptide 9 is illustrated as a “perfect” amphipathic helix (N-terminal message segment to the left), with a calculated Connolly surface. The surface has been colorized to indicate hydrophilic (red) and hydrophobic (blue) surfaces. Idealized “Class A” and “Class L” amphipathic helices are shown illustrated as Edmund diagrams (end view) with the same color scheme.--

Please replace the paragraph at page 11, line 11 with the following re-written paragraph:

**--Glycopeptide Design Principles.** Three series of glycosylated  $\beta$ -endorphin analogs have been designed and synthesized for study. The peptide sequences were not homologous to  $\beta$ -endorphin, but the C-terminal regions were designed to produce amphipathic helix conformations, and bear one or more serine glycosides. A complete blood-brain barrier study of these compounds in mice will be published separately,<sup>i</sup> but some of the most salient BBB results will be presented here, along with opioid binding and functional assays. It is noteworthy that some of the much longer endorphin glycopeptide analogs penetrate the mouse BBB at higher rates than the much shorter enkephalin glycopeptide analogs. In this study, we will focus on the design and conformational analysis of representative  $\beta$ -endorphin glycopeptide analogs in water, TFE-water mixture, SDS micelles and bicelles determined by

<sup>2</sup>D-<sup>1</sup>H NMR and circular dichroism (CD). The organic solvent trifluoroethanol (TFE) has traditionally been used to promote secondary structure formation.<sup>ii</sup> Later, the use of detergent micelles was proposed to study peptide-membrane interactions.<sup>iii</sup> Recently, in order to better mimic the flatter membrane environment, the use of phospholipid bicelles was proposed, and is gaining momentum because of its advantages over organic solvents and micelles.<sup>iv</sup> The bicelles used in the NMR studies are disk-shaped aggregates formed by mixing long-chained phospholipids, such as dimyristoylphosphatidylcholine ~~dimyristoylphosphatidylcholine~~ (DMPC) which form a bilayer domain disk, along with short-chained surfactant phospholipids, such as dihexanoylphosphatidylcholine (DHPC) that seal the edges of the bilayer.<sup>30b,v</sup> Unlike micelles, which show extreme positive curvature, the phospholipid bicelles constitute a true fluid membrane bilayer segment with a very low curvature (Figure 1). It has been shown that while some membrane-bound enzymes lose their activity in micellar solution, activity is often retained when bound to phospholipid bicelles.<sup>vi</sup> It has also been shown previously that Met-enkephalin shows a different conformational ensemble in the presence of the more fluid bicelles than in a micelle environment.<sup>vii</sup> Conformational studies of cell-penetrating peptides in SDS micelle and bicelle systems show that these peptides adopt very similar structure in both systems, but the position of the peptides in a micelle differs significantly from the position in the phospholipid bilayer.<sup>viii</sup> Thus, in order to understand the behavior of the glycopeptides that traverse the BBB, it is important to study the conformational properties of the glycopeptides in TFE-water mixtures as well as in membrane mimicking micelles and bicelles.--